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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,449	10/31/2003	Karla M. Robotti	10030218-1	2836

7590	09/19/2007
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EXAMINER	
CORDERO GARCIA, MARCELA M	

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
09/19/2007	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

Application No.

10/699,449

Applicant(s)

ROBOTTI, KARLA M.

Examiner

Marcela M. Cordero Garcia

Art Unit

1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 30 April 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) 24-26 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

This Office Action is in response to the reply received on April 30, 2007.

Claims 1-26 are pending in the application.

Claims 1-23 are presented for examination on the merits. Claims 24-46 are withdrawn as not drawn to the elected group. Applicant previously elected the species wherein the nucleophile is an amine moiety, wherein the linker includes a photocleavable group having the structure (IV), wherein the deglycosylated protein is released from the solid support by exposing the resin bound deglycosylated protein to light, and wherein the released proteins are subjected to mass spectrometric analysis. Claims 1-11 and 14-19 are readable thereon. Claims 1-11 and 14-19 have been searched and examined and found free of the prior art with respect to Applicant's elected species (however, please see 112 1<sup>st</sup> rejection below). Please note that no claims drawn to this species are written in independent form and therefore, as drafted, the claims are not allowable.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The

MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

***In the instant case, the claims are drawn to a method comprising:***

***a) obtaining a mixture comprising glycosylated protein and unglycosylated proteins, wherein the glycosylated protein comprises a protein having a glycosylation site and a glycosyl group bound to the protein via the glycosylation site,***

***b) contacting the mixture with a resin, wherein the resin comprises a nucleophile bound to a solid support via a linker, said contacting done under conditions sufficient to remove the glycosyl group by  $\beta$ -elimination from the glycosylated protein to yield a deglycosylated protein having an unsaturated intermediate at the deglycosylation site, the deglycosylated protein bound to the solid support via the unsaturated intermediate at the deglycosylation site;***

***c) rinsing the bound deglycosylated protein, thereby removing unglycosylated proteins;***

***d) releasing the deglycosylated protein from the solid support.***

With regards to the "glycosylated protein" term, this is a very broad generic statement drawn to any proteins of any composition and molecular weight comprising at

least one glycosylated site, there exists a plethora of such compounds, which are not adequately described and/or represented in the examples. By the same token, the preamble is drawn to "a method" comprising the instantly claimed steps, however, it does not describe what kind of a method it is, e.g., a method for analyzing glycosylated proteins, a method for isolating glycosylated proteins, etc. By the same token, the term "nucleophile" is defined in the disclosure as a reactive group that has an available electron pair with which it attacks another atom to form a new covalent bond (e.g., page 16, lines 29-33). Typical nucleophiles are taught by the disclosure to include thiol groups, amine groups, and hydroxyl groups, and any other nucleophilic group capable of reacting to covalently bind the deglycosylated protein to the solid support. (see, e.g., page 17, lines 10-15). The claims are drawn, not only to any nucleophile attached to any kind of resin, but also to any kind of glycosylation site, disclosed in the specification as "monosaccharide or oligosaccharide group of a glycosylated protein" (e.g. page 5, lines 10-11) and any kind of glycosylated proteins (e.g., O-glycosylated, N-glycosylated, C-mannosylated, phosphoglycosylated) of any molecular weight and composition. In addition, at claim 17, the term tag is defined as a mass tag, a fluorescent tag, and affinity tag, or a chemical group having a specific reactivity, which is therefore not describe as having any core except for an extremely broad functional reactivity and therefore does not provide adequate written description. A mere statement that such nucleophiles attached to resins would be desirable for conjugation of glycosylated proteins of any kind and in any kind of biological source (see disclosure at page 18, lines 1-5) does not sufficiently provide ample written description pages describing the full breadth of the glycosylated proteins and nucleophiles within the instant method as instantly claimed, including the tags of claim 17. The specification does provide examples of what qualify as compounds of the claimed invention: a single example is

provided by Applicant, describing a separation of an unspecified protein sample that was digested, but for which the molecular weight or any other chemical characteristics were not provided (see, page 22, lines 24-28. As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 1 is a broad generic with respect all possible methods encompassed by the claims. The possible structural variations within the glycosylated peptides are limitless to any class of proteins having any molecular weight but including a monosaccharide or oligosaccharide therein. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some structural characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of complex mixtures of peptides in a variety of biological samples, peptides of different molecular weights with distinct monosaccharides or oligosaccharides as the glycosyl group, distinct linking such as O-glycosylation or N-glycosylation, C-mannosylation, phosphoglycosylation, and many others not even yet discovered, as taught by Spiro et al. (page 52R, column 1, last paragraph and column 2), different nucleophiles, different tags, and so forth. See e.g., Wells et al. which teaches that some of O-GlcNAc-modified residues are more resistant to  $\beta$ -elimination than phosphorylated sites, which implies that the method would not work in cases where phosphorylated sites would react more

easily than glycosylated sites (e.g., Wells et al., page 793, last paragraph and page 795, column 1 and column 2, lines 1-9). The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

### ***Summary of Applicants Arguments***

Applicants arguments are summarized as follows:

1) The Applicants firstly note that the specification indicates that targets will be found "in a biological sample" (specification, page 18, first paragraph). As such, the target proteins do not include an infinite number of glycopeptides of any mass or composition, nor an infinite number of saccharides with any possible functional group attached by an endless variety of chemical bonds, such as might be found in a chemical library.

2) The variety of types of glycosylation linkages found in biological samples has been well characterized and experimentation required to separate the various types is

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within realm of routine experimentation. The technique is applicable to the separation of any sample containing a mixture of glycosylated and deglycosylated proteins, including O-glycosylated proteins, N-glycosylated proteins, C-mannosylated, phosphoglycosylated, etc. The  $\beta$ -elimination reactions are known to those skilled in the art without undue experimentation.

3) With respect to complex mixtures of proteins found in biological samples, and cases in which the target may be rare, the instant specification describes optionally subjecting the biological sample to one or more separation processes, such as digesting with one or more proteases before contacting the mixture with the resin. In this embodiment, glycosylated or unglycosylated proteins in the mixture have a molecular weight of about 5000 Da or less after digestion. In typical embodiments, prior to contacting the mixture with the resin, the mixture may be treated to dephosphorylate the proteins in the mixture, e.g., by treating the mixture with a phosphatase to remove phosphate moieties from the proteins. Conditions and protocols for performing the dephosphorylation are known in the art.

4) Regarding variation in mass of potential target proteins, the specification throughout describes the result of the  $\beta$ -elimination reaction as a target protein covalently bonded to the solid support. As is well known in the art, the covalent bond is the strongest known organic chemical bond and, as such, provides for a very wide toleration of mass in the target protein. As such, the methods described by the instant specification are sufficient for the isolation of glycosylated proteins in biological samples.

5) With respect to the identities of the saccharide group, the specification indicates that the saccharide monomer subunits typically are selected from N-acetyl glucosamine, mannose, and muramic acid, sialic acids, and N-acetyl galactosamine, *although other saccharide monomer subunits known in the literature of glycosylated proteins may be present*. Chemical linkages typically encompass glycosylated proteins comprising O-linked sugar residues, such as O-linked N-acetyl glucosamine. Each of the described glycosyl groups is susceptible to  $\beta$ -elimination from the protein to which it is bound under the conditions under which the mixture is contacted with the resin (e.g., page 17, lines 20-31).

### ***Response to Arguments***

Applicants arguments have been fully considered by Examiner, but not deemed persuasive because:

With respect to **1)**: Examiner reiterates that the claims, as drafted, are drawn to a genus of methods which encompasses an uncountable number of glycopeptides of any mass or composition, including any kind of mono- or oligo-saccharides bonded therein and reacting with any nucleophile attached to a resin as set forth in the rejection above. Moreover, please note that the limitation "in a biological sample" is not included within the claims limitations and therefore does not limit the instant claims.

With regard to **2)**: Examiner has not been provided any evidence regarding the statement that the variety of types of glycosylation linkages found in biological samples

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has been well characterized and experimentation required to separate the various types is within realm of routine experimentation including separation of any sample containing a mixture of glycosylated and deglycosylated proteins, including O-glycosylated proteins, N-glycosylated proteins, C-mannosylated, phosphoglycosylated using  $\beta$ -elimination reactions known to those skilled in the art without undue experimentation. Therefore the argument is not deemed persuasive.

Regarding the arguments in section 3): Applicant is arguing the limitations with regards to treatment of complex mixtures (such as most biological samples): --subjecting the mixture to digestion in order to obtain a mixture with molecular weight of 5000 Da or less-- and --dephosphorylation of proteins in the mixture, e.g., by treating the mixture with a phosphatase to remove phosphate moieties from the proteins--. However, these limitations are not included within the instant claims and therefore are not persuasive regarding the broad method as drafted.

Applicants arguments is 4) are not substantiated by any evidence regarding covalent linkages formed by b-elimination and e.g., tertiary structure in large proteins (e.g., 200 kDa). No evidence was provided for the statement "the covalent bond is the strongest known organic chemical bond and, as such, provides for a very wide toleration of mass in the target protein". Therefore, the arguments are not deemed persuasive.

In 5): The instant claims do not encompass Applicant's alleged limitations, which are selected from the disclosure (but not part of the instantly claimed subject matter). The instant claims are drawn to any saccharide attached to any protein, wherein the

saccharide is a monosaccharide or *an oligosaccharide* as set forth in the rejection above. Therefore, the arguments are not deemed persuasive.

### **Conclusion**

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

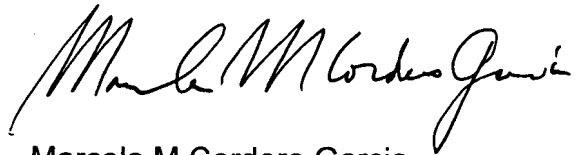
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M. Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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